

B5

לשימוש הלשכה
For Office Use

חוק הפטנטים, תשכ"ז - 1967
PATENTS LAW, 5727-1967

ב ק ש ה ל פ ט נ ט
Application For Patent

84021/2	מספר: Number
29.9.87	תאריך: Date
הוקדם/נדחה Ante/Post-dated	

אני, (שם המבקש, מענו ולגבי גוף מאוגד - מקום התאגדותו)
I (Name and address of applicant, and in case of body corporate-place of incorporation)

NOVO NORDISK A/S
Novo Alle
DK-2880 Bagsvaerd
Denmark

בעל אמצאה מכה ~~אמצאה~~ ~~right of law~~ an assignment העברה
Owner, by virtue of
שמה הוא of an invention the title of which is

תרכבות פיפרידין, הכנתן ותכשירי רוקחות המכילים אותן (בעברית)
(Hebrew)

Piperidine compounds, their preparation and pharmaceutical compositions containing them (באנגלית)
(English)

הבקש בואת כי ינתן לי עליה פטנט hereby apply for a patent to be granted to me in respect thereof.

מבקש בואת כי ינתן לי עליה פטנט

* בקשת חלוקה - Application of Division		* בקשת פטנט מוסף - Application for Patent Addition		* דרישה דין קדימה Priority Claim		
מבקשת פטנט from Application	מס' / No.	לבקשה/לפטנט to Patent/Appl.	מס' / No.	מספר/סימן Number/Mark	תאריך Date	מדינת האגוד Convention Country
No. _____ dated _____	מס' _____ מיום _____	No. _____ dated _____	מס' _____ מיום _____	5232/86 3234/87	3.11.86 25.6.87	Denmark Denmark
P.O.A.: general T.M. 73127		* יפוי כח: כללי הוגש בעניין קודם				
המען למסירת מסמכים בישראל Address for Service in Israel						
DR. REINHOLD COHN AND PARTNERS Patent Attorneys P.O.B. 4060, Tel-Aviv		C: 73053				
חתימת המבקש Signature of Applicant		היום 28th בחודש Sept. 1987 of the year of This				
For the Applicants, DR. REINHOLD COHN AND PARTNERS By: —		לשימוש הלשכה For Office Use				
		תאריך הפרסום: 21-02-1988 תאריך ההגשה: _____				

טופס זה, כשהוא מוטבע בחותם לשכת הפטנטים ומשולם במספר ובתאריך ההגשה, הנו אישור להגשת הבקשה שפרטיה רשומים לעיל.
This form, impressed with the Seal of the Patent Office and indicating the number and date of filing, certifies the filing of the application the particulars of which are set out above.

תרכובות פפרידין, הכנתן ותכשירי רוקחות
המכילים אותן

Piperidine compounds, their preparation and
pharmaceutical compositions containing them

A/S FERROSAN

C: 73053

- 1a -

The present invention relates to therapeutically active piperidine compounds, a method of preparing the same and to pharmaceutical compositions comprising the compounds. The novel compounds are useful in the treatment of anoxia, ischemia, migraine and epilepsy.

It is well known that accumulation of calcium in the brain cells (calcium overload) is seen after periods of uncontrolled hyperactivity in the brain, such as after convulsions, migraine, anoxia and ischemia. As the concentration of calcium in the cells is of vital importance for the regulation of cell function, an uncontrolled high concentration of the cell calcium will lead to, or indirectly cause the symptoms and possibly also the degenerative changes combined with the above diseases.

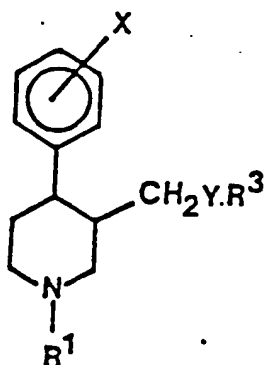
Therefore calcium overload blockers selective for brain cells will be useful in the treatment of anoxia, ischemia, migraine and epilepsy.

Well known calcium antagonists such as nifedipine, verapamil and diltiazem have activity against peripheral calcium uptake, e.g. in blood vessels and the heart, however have shown only very low activity against calcium overload in brain cells.

Accordingly it is an object of the invention to provide novel pharmaceutical compositions having activity against calcium overload in brain cells.

The novel compositions of the invention comprise piperidine compounds having the general formula I

- 1b -



(I)

wherein

R³ is 3,4-methylenedioxyphenyl, phenyl, naphthyl or benzothiazolyl, which are optionally substituted with one or more C₁₋₆-alkyl, C₁₋₆-alkoxy group, C₃₋₈-cycloalkyl, C₃₋₅-alkylene or benzyloxy,

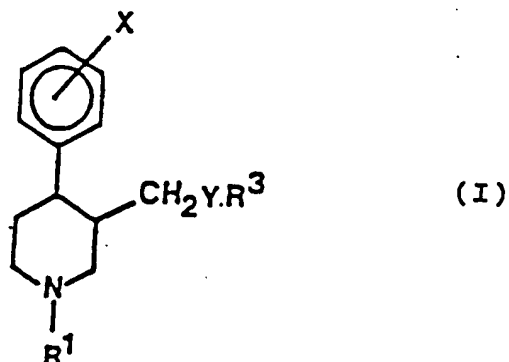
R¹ is hydrogen or straight or branched C₁₋₈-alkyl, C₁₋₈-alkoxy-C₁₋₈-alkyl, C₁₋₇-cycloalkyl, phenoxy-C₁₋₈-alkyl, C₁₋₈-alkenyl, or C₁₋₈-cycloalkylalkyl,

X is hydrogen or halogen, and wherein

Y is O or S

and a salt thereof with a pharmaceutically acceptable acid.

In accordance with another aspect the present invention provides novel piperidine compounds having the general formula (I)



wherein

R^3 is 3,4-methylenedioxyphenyl, phenyl, naphthyl or benzothiazolyl which are optionally substituted with one or more C_{1-6} -alkyl, C_{1-6} -alkoxy group, C_{3-8} -cycloalkyl, C_{3-5} -alkylene or benzyloxy,

R^1 is straight or branched C_{5-8} -alkyl, C_{1-8} -alkoxy- C_{4-8} -alkyl, C_{4-7} -cycloalkyl, phenoxy- C_{3-8} -alkyl, C_{4-8} -alkenyl, or C_{4-8} -cycloalkylalkyl, or R^1 may also be hydrogen or C_{1-4} -alkyl when R^3 is phenyl substituted with two or more of C_{3-8} -cycloalkyl, benzyloxy or C_{3-5} -alkylene, or when R^3 is naphthyl or benzothiazolyl substituted with two or more C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{3-8} -cycloalkyl, benzyloxy or C_{3-5} -alkylene,

X is hydrogen or halogen, and wherein

Y is O or S

and a salt thereof with a pharmaceutically acceptable acid.

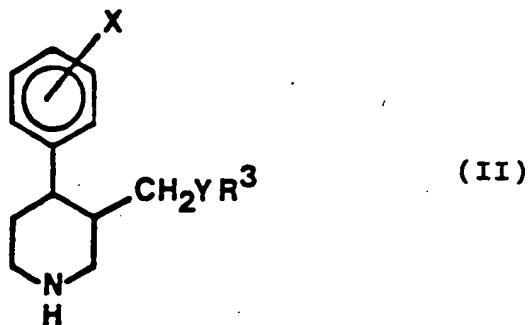
Examples of such salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate, or similar pharmaceutically-acceptable inorganic or organic acid addition salts.

The invention also relates to a method of preparing the above mentioned compounds. This method comprises

a) reacting a compound having the general formula II

5

10

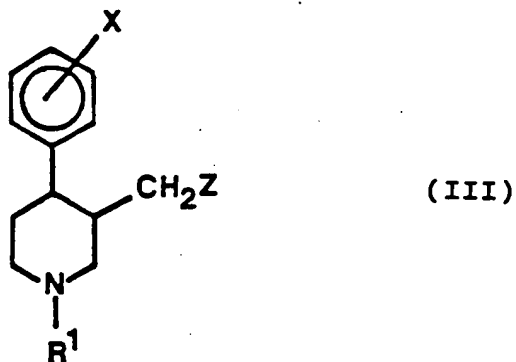


wherein R^3 , X and Y have the meanings defined above, with a compound having the general formula R^1-Z , wherein Z is a leaving group such as halogen and R^1 has the meaning defined above,

b) reacting a compound having the general formula III

20

25



wherein R^1 and X have the meanings defined above, and Z is a leaving group, with a compound having the general formula R^3-YH , wherein Y is O or S and R^3 has the meaning defined above.

The pharmacological properties of the compounds of the invention can be illustrated by determining their capability to inhibit calcium uptake into brain synaptosomes.

PRINCIPLE

Depolarization of neuronal membranes leads to an opening of so-called 'voltage operated calcium channels' (VOC) in the membranes which allows a massive influx of calcium from the extracellular space. A crude synaptosomal preparation (so-called P_2 fraction) contains small vesicles surrounded by neuronal membrane and it is possible in such a preparation to study a depolarization-induced opening of VOC. In the present model ^{45}Ca influx is induced in the synaptosomes by depolarization with elevated potassium concentrations, and the effect of test substances on this stimulated uptake is studied (Nachshen, D.A. and Blaustein, M.P., Mol. Pharmacol., 16, 579 (1979)).

ASSAY

A male Wistar rat is decapitated and the cerebral cortex removed and homogenized in 20 ml. of ice-cold 0.32 M sucrose using a glass homogenizer with a teflon pestle. All subsequent steps for isolation of synaptosomes are done at 0-4°C. The homogenate is centrifuged at 1000 x g for 10 min and the resulting supernatant is re-centrifuged at 18000 x g for 20 min. This pellet (P_2) is resuspended in 0.32 M sucrose (10 ml per g of original tissue) with a teflon pestle.

Aliquots (0.050 ml) of this crude synaptosomal suspension are added to glass tubes containing 0.625 ml of NaCl buffer (136 mM NaCl, 4 mM KCl, 0.35 mM CaCl_2 , 1.2 mM MgCl_2 , 20 mM Tris HCl, 12 mM glucose, pH 7.4) and 0.025 ml of various drug solutions in 48% Ethanol. The tubes are pre-incubated for 30 min on ice and then for 6 min at 37°C in a water bath.

The uptake is immediately initiated by adding 0.4 ml of $^{45}\text{CaCl}_2$ (specific activity = 29-39 Ci/g; 0.5 Ci/assay), in 145 mM NaCl for non-depolarized samples and in 145 mM KCl for depolarized samples. The incubation is continued for 15 s.

The uptake is terminated by rapid filtration through GF-C glass fiber filters which are washed three times with 5 ml of a cold solution containing 145 mM KCl, 7 mM EGTA and 20 mM Tris HCl, pH 7.4. The amount of radioactivity on the filter disc is determined by liquid scintillation spectrometry.

15 TEST PROCEDURE

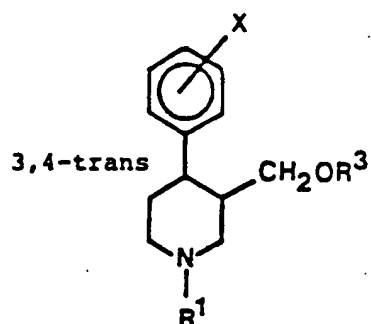
Test substances are dissolved in 10 ml of 48% ethanol at a concentration of 0.44 mg/ml. Dilution are made in 48% ethanol to give final concentrations of 0.1, 0.3, 1, 3 and 10 $\mu\text{g/ml}$. Experiments are performed in duplicate. Controls for depolarized and nondepolarized samples are included in the assay and test substances are only tested in depolarized samples. 25-75% inhibition of stimulated uptake must be obtained before calculating the IC_{50} value.

25 RESULTS

The test value will be given as IC_{50} (the concentration ($\mu\text{g/ml}$) of test substance which inhibit 50% of stimulated uptake of ^{45}Ca (uptake in depolarized samples corrected for basal uptake in nondepolarized samples)). The IC_{50} value is estimated from dose response curves.

35 Test results obtained by testing some compounds of the present invention will appear from the following table 1.

Table 1



15

20

25

30

R^1	R^3	X	optic form	IC_{50} $\mu\text{g/ml}$
$-(\text{CH}_2)_3\text{CH}_3$		4-F	(-)	1,9
$-(\text{CH}_2)_3\text{CH}_3$		4-F	(-)	2,3
$-\text{CH}(\text{CH}_3)_2$		4-F	(-)	4,3
$-(\text{CH}_2)_7\text{CH}_3$		4-F	(-)	2,2
$-(\text{CH}_2)_4\text{CH}_3$		4-F	(-)	1,5
$-\text{CH}_2\text{CH}_3$		4-F	rac	2,5
$-\text{CH}_2-\text{CH}=\text{CH}_2$		4-F	(-)	0,8
$-(\text{CH}_2)_4\text{CH}_3$		H	(+)	2.4
$-(\text{CH}_2)_4\text{CH}_3$		4-F	(-)	0.4
Nifedipin *				26
Verapamil *				16
Diltiazem *				>90

35 * Well known calcium antagonists

* * * * *

The compound of the invention, together with a conventional adjuvant, carrier, or diluent, and if desired in the form of a pharmaceutically-acceptable acid addition salt thereof, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets of filled capsules, or liquids, such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective calcium overload blocking amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing ten (10) milligrams of active ingredient or, more broadly, ten (10) to hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of this invention can thus be used for the formulation of pharmaceutical preparations, e.g. for oral and parenteral administration to mammals including humans, in accordance with conventional methods of galenic pharmacy.

Conventional excipients are such pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral or enteral application which do not deleteriously react with the active compounds.

Examples of such carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Ampoules are convenient unit dosage forms.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch, are particularly suitable for oral application. A syrup, elizir of the like can be used in cases where a sweetened vehicle can be employed.

Generally, the compounds of this invention are dispensed in unit form comprising 0.05-100 mg in a pharmaceutically acceptable carrier per unit dosage.

The dosage of the compounds according to this invention is 0.1-300 mg/day, preferably 10-100 mg/day, when administered to patients, e.g. humans, as a drug.

A typical tablet which may be prepared by conventional tabletting techniques contains:

	Active compound	5.0 mg
	Lactosum	67.8 mg Ph.Eur.
	Avicel TM	31.4 mg
35	Amberlite TM IRP 88	1.0 mg
	Magnesii stearas	0.25 mg Ph.Eur.

Due to the high calcium overload blocking activity , the compounds of the invention are extremely useful in the treatment symptoms related to an accumulation of calcium in brain cells of mammals , when administered in an amount effective
5 for blocking calcium overload in brain cells . The important calcium overload blocking activity of compounds of the invention includes both activity against anoxia, ischemia, migraine and epilepsy . The compounds of the invention may accordingly be administered to a subject, e.g., a living
10 animal body, including a human, in need of a calcium overload blocker , and if desired in the form of a pharmaceutically-acceptable acid addition salt thereof (such as the hydrobromide, hydrochloride, or sulfate, in any event prepared in the usual or conventional manner, e.g., evaporation to
15 dryness of the free base in solution together with the acid), ordinarily concurrently, simultaneously, or together with a pharmaceutically-acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parenteral (including
20 subcutaneous) route, in an effective calcium overload blocking amount, and in any event an amount which is effective for the treatment of anoxia, ischemia, migraine or epilepsy due to their calcium overload blocking activity. Suitable dosage ranges are 1-200 milligrams daily, 10-100 milligrams
25 daily, and especially 30-70 milligrams daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and the preference and experience of
30 the physician or veterinarian in charge.

The invention will now be described in further detail with reference to the following examples:

Example 1

(-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-pentylpiperidine hydrochloride

5
10g of (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-piperidine hydrochloride in 250 ml 99.9% ethanol was mixed with 50 ml 1-bromopentane and 20 g potassium carbonate. The mixture was refluxed for 3 hours and
10 was subsequently cooled to room temperature. 25 ml acetone and 25 ml diethylether was added to the solution. The precipitate was filtered off and the filtrate was evaporated in vacuo. 20 ml 4N NaOH was added to the residue, and the resulting mixture was extracted 3 times with diethyl ether.
15 The combined ether phases were dried over potassium carbonate, filtered, the filtrate was acidified with conc. hydrochloric acid to pH 2, and the filtrate was evaporated in vacuo. The resulting oil was dissolved in acetone and crystals precipitated by addition of ether and after cooling at
20 4°C over night. The title compound was filtered off and dried giving 10.1 g of the title compound. M.p. 153.6°C.

The following compounds were prepared in exactly the same manner from (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-piperidine hydrochloride and the
25 corresponding alkyl bromide, alkoxyalkyl bromide, cycloalkyl bromide, aryloxyalkyl bromide, or alkenyl bromide.

(-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-ethylpiperidine hydrochloride M.p. 237-238°C by
30 refluxing the reaction mixture for 24 hours.

(-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-propylpiperidine hydrochloride M.p. 198.3°C by
35 refluxing the reaction mixture for 7 hours.

- (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-butylpiperidine hydrochloride M.p. 190-191°C by refluxing the reaction mixture for 7 hours.
- 5 (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-octylpiperidine hydrochloride M.p. 167.3°C by refluxing the reaction mixture for 72 hours.
- 10 (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-isopentylpiperidine hydrochloride M.p. 152.6°C by refluxing the reaction mixture for 6 hours.
- 15 (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-(4-phenoxybutyl)-piperidine hydrochloride as an oil by refluxing the reaction mixture for 240 hours.
- 20 (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-hexylpiperidine hydrochloride M.p. 107.1°C by refluxing the reaction mixture for 24 hours.
- 25 (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-(3-phenylpropyl)-piperidine hydrochloride as an oil by refluxing the reaction mixture for 3.5 hours.
- 30 (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-(2-ethylhexyl)-piperidine hydrochloride as an oil by refluxing the reaction mixture for 240 hours.*
- 35 (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-(3,3-dimethylbutyl)-piperidine hydrochloride M.p. 226.7°C by refluxing the reaction mixture for 336 hours.*
- (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-cyclohexyl-piperidine hydrochloride M.p. 140.2°C by refluxing the reaction mixture for 330 hours.*

- (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-heptyl-piperidine hydrochloride M.p. 146.8°C
by refluxing the reaction mixture for 6 hours.
- 5 (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-cyclopentyl-piperidine hydrochloride M.p. 227.7°C
by refluxing the reaction mixture for 7 hours.
- 10 (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-allyl-piperidine hydrochloride M.p. 162.2°C
by refluxing the reaction mixture for 24 hours.
- 15 (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-cyclopropylmethylpiperidine hydrochloride M.p.
175.5°C by refluxing the reaction mixture for 24 hours.
- 20 (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-cycloheptyl-piperidine hydrochloride as an glas
M.p. 53.7°C by refluxing the reaction mixture for 190
hours.* and **
- 25 (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-(2-ethoxyethyl)-piperidine hydrochloride as an
glass M.p. 49.5°C by refluxing the reaction mixture for 6
hours.
- 30 (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-(2-methoxymethyl)-piperidine hydrochloride M.p.
164.7°C by refluxing the reaction mixture for 48 hours.
- (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-(2-trans-butenyl)-piperidine hydrochloride M.p.
195.5°C by refluxing the reaction mixture for 3 hours.
- 35 (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-(3-butenyl)-piperidine hydrochloride M.p.
198.6°C by refluxing the reaction mixture for 288 hours.

(-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-(5-hexenyl)-piperidine hydrochloride M.p. 123.1°C by refluxing the reaction mixture for 3 hours.

5 (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-(4-pentenyl)-piperidine hydrochloride M.p. 177.7°C by refluxing the reaction mixture for 3 hours.

10 (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-(3-methyl-butenyl)-piperidine hydrochloride M.p. 239.2°C by refluxing the reaction mixture for 4.5 hours.

* The crude compound was purified on a silicagel column using 99.9% ethanol as eluent. The eluent solution was acidified and the title compound was isolated as described above, 15 i.e. by evaporation, dissolution in acetone and precipitation by addition of diethyl ether.

20 ** 1-Butanol was used as solvent instead of ethanol.

(-)-cis-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-pentylpiperidine hydrochloride M.p. 195.3°C and (+)-cis-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-1-pentylpiperidine hydrochloride M.p. 193.7°C were 25 prepared exactly as described above from pentyl bromide, and (-)-cis-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-piperidine hydrochloride and (+)-cis-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxy-methyl)-piperidine hydrochloride respectively.

30

Example 2

(-)-trans-1-butyl-4-(4-fluorophenyl)-3-(4-methoxyphenoxy-methyl)-piperidine hydrochloride

35

(-)-trans-1-butyl-4-(4-fluorophenyl)-3-(4-methoxyphenoxy-methyl)-piperidine hydrochloride M.p. 163-165°C was prepared

exactly as described in example 1 from (-)-trans-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride and butyl bromide by refluxing for 120 hours.

- 5 The following compounds were prepared in exactly the same manner from (-)-trans-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride and the corresponding alkyl bromide or cycloalkyl bromide.
- 10 (-)-trans-1-propyl-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride M.p. 196-197°C by refluxing the reaction mixture for 7 hours.
- 15 (-)-trans-1-ethyl-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride M.p. 190-191°C by refluxing the reaction mixture for 170 hours.
- 20 (-)-trans-1-isopropyl-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride as an oil by refluxing the reaction mixture for 210 hours.
- 25 (-)-trans-1-(2-(4-methoxyphenoxyethyl))-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride as an oil by refluxing the reaction mixture for 48 hours.
- 30 (-)-trans-1-pentyl-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride as a glass M.p. 53.5°C by refluxing the reaction mixture for 8 hours.
- 35 (-)-trans-1-heptyl-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride M.p. 138.1°C by refluxing the reaction mixture for 8 hours.
- 35 (-)-trans-1-cyclohexyl-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride M.p. 220.3°C by refluxing the reaction mixture for 330 hours.**

** 1-Butanol was used as solvent instead of ethanol.

Example 3

5 trans-1-propyl-4-(4-fluorophenyl)-3-(4-t-butylphenoxy-
methyl)-piperidine hydrochloride

trans-1-propyl-4-(4-fluorophenyl)-3-(4-t-butylphenoxy-
methyl)-piperidine hydrochloride M.p. 221.1°C was prepared
10 exactly as described in example 1 from trans-4-(4-fluoro-
phenyl)-3-(4-t-butylphenoxy-methyl)-piperidine hydrochloride
and propyl bromide by refluxing for 96 hours.

The following compounds were prepared in exactly the same
15 manner from trans-4-(4-fluorophenyl)-3-(4-t-butylphenoxy-
methyl)-piperidine hydrochloride and the corresponding alkyl
bromide.

trans-1-ethyl-4-(4-fluorophenyl)-3-(4-t-butylphenoxy-methyl)-
20 piperidine hydrochloride M.p. 220.6°C.

trans-1-butyl-4-(4-fluorophenyl)-3-(4-t-butylphenoxy-methyl)-
piperidine hydrochloride M.p. 183.1°C.

25

Example 4

(-)-trans 3-(2-Cyclohexylphenoxy-methyl)-4-(4-fluorophenyl)-
1-methyl-piperidine, HCl.

30 5.13g 2-cyclohexylphenol was dissolved in dry DMF. 1.5g NaH
(55% oil dispersion) was washed with ether and subsequent-
ly added slowly to the solution. When gas evolution had
ceased, 6.4 g of (-) trans 3-chloromethyl-4-(4-fluorophenyl)-
1-methylpiperidine, was slowly added and the mixture reflu-
35 xed for 5h. Subsequently the mixture was left at room tem-
perature overnight, evaporated to dryness in vacuo. The
residue was dissolved in dilute NaOH and extracted several

times with ether. The ethereal layers were dried with K_2CO_3 , evaporated to dryness and extracted once more from NaOH with ether. The ether layer was extracted with dilute HCl, the acid solution evaporated to dryness and the residue
 5 further purified on a silicagel column using $CHCl_3/CH_3OH$ (9/1) as eluent. The compound was isolated from the eluent by evaporation. m.p. $64.9^\circ C$ (hard glass)

The following compounds were prepared in the same manner
 10 from (-) trans-3-chloromethyl-4-(4-fluorophenyl)-1-methylpiperidine and the appropriate phenol.

-trans 4-(4-Fluorophenyl)-1-methyl-3-(5,6,7,8,-tetrahydro-2-naphthoxymethyl)-piperidine, HCl. m.p. $198.5^\circ C$.
 15

-trans 3-(4-Benzyloxyphenoxyethyl)-4-(4-fluorophenyl)-1-methylpiperidine, HCl. m.p. $112.5^\circ C$.

-trans 3-(4-Benzyloxy-3-methoxyphenoxyethyl)-4-(4-fluorophenyl)-1-methylpiperidine, HCl. m.p. $59.6^\circ C$ (hard glass)
 20

-trans 4-(4-Fluorophenyl)-1-methyl-3-(2-naphthoxymethyl)-piperidine, HCl. m.p. $214.4^\circ C$.

25

Example 5

A): -trans 3-(2-Cyclohexylphenoxyethyl)-4-(4-fluorophenyl)-piperidine, HCl was prepared by means of alpha-chloroethyl-chloroformate using the method described in J.Org.Chem.
 30 1984:49:2081 (R.A. Olofson, J.T. Martz, J.P. Senet, M. Piteau and T. Malfroot), m.p. $216.7^\circ C$.

The following compounds were prepared in exactly the same manner by dealkylation of the corresponding N-methyl-compound.
 35

(+ -) trans 3-(4-Benzoyloxyphenoxymethyl)-4-phenylpiperidine, HCl. m.p. 132.4°C.

5 (-) trans 4-(4-Fluorophenyl)-3-(5,6,7,8,-tetrahydro-2-naphthoxymethyl)-piperidine, HCl. m.p. 55.1°C (hard glass)

(-) trans 3-(4-Benzoyloxyphenoxymethyl)-4-(4-fluorophenyl)-piperidine. m.p. 132.7°C.

10 (-) trans 3-(2-Benzothiazolylthiomethyl)-4-(4-fluorophenyl)-piperidine, HCl. m.p. 72.2°C (hard glass)

(-) trans 4-(4-Fluorophenyl)-3-(2-naphthoxymethyl)-piperidine, HCl. m.p. 238.6°C.

15

B): The following compounds were prepared from the corresponding piperidine and alkyl bromide in exactly the same manner as described in example 1.

20 (-) trans 3-(2-Cyclohexylphenoxymethyl)-4-(4-fluorophenyl)-1-pentylpiperidine, HCl. m.p. 210.3°C. Reaction time 18h.

(+) trans 3-(3,4-Methylenedioxyphenoxymethyl)-1-pentyl-4-phenylpiperidine, HCl. m.p. 175.0°C. Reaction time 2.5h.

25

(+ -) trans 3-(4-Benzoyloxyphenoxymethyl)-1-pentyl-4-phenylpiperidine, HCl. m.p. 139.5°C. Reaction time 17h.

30 (+ -) trans 1-Allyl-3-(4-benzoyloxyphenoxymethyl)-4-phenylpiperidine, HCl. m.p. 212.1°C. Reaction time 3.5h. Equimolar amounts of piperidine-compound and allyl bromide was used.

(-) trans 3-(4-Methoxyphenoxymethyl)-1-pentyl-4-phenylpiperidine, HCl. m.p. 138.7°C. Reaction time 18h.

35

- (-) trans 1-Allyl-3-(4-methoxyphenoxyethyl)-4-phenylpiperidine, HCl. m.p. 197.5°C. Reaction time 1.5h. Equimolar amounts of allyl bromide and piperidine-compound was used.
- 5 (+) trans 3-(4-Methoxyphenoxyethyl)-1-pentyl-4-phenylpiperidine, HCl. m.p. 138.7°C. Reaction time 18.5h.
- (+) trans 1-Allyl-3-(4-methoxyphenoxyethyl)-4-phenylpiperidine, HCl. m.p. 195.9°C. Reaction time 20.5h. Equimolar
10 amounts of allyl bromide and piperidine-compound was used.
- (-) trans 4-(4-Fluorophenyl)-1-pentyl-3-(5,6,7,8-tetrahydro-2-naphthoxyethyl)-piperidine, HCl. m.p. 55.3°C (hard glass). Reaction time 2h. The crude product was purified on
15 a silicagel column, CHCl₃/CH₃OH (9/1) as eluent.
- (-) trans 3-(2-Benzothiazolylthiomethyl)-4-(4-fluorophenyl)-1-pentylpiperidine, HCl. m.p. 199.9°C. Reaction time 7h.
- 20 (-) trans 4-(4-Fluorophenyl)-3-(2-naphthoxyethyl)-1-pentylpiperidine, HCl. m.p. 54.6°C (hard glass). Reaction time 4.5h. The crude product was purified on a silicagel column with CHCl₃/CH₃OH (9/1) as eluent.
- 25 (-) trans 1-Butyl-4-(4-fluorophenyl)-3-(5,6,7,8-tetrahydro-2-naphthoxyethyl)-piperidine, HCl. M.p. 154.3°C. Reaction time 2.5 h.
- (-) trans 4-(4-Fluorophenyl)-1-propyl-3-(5,6,7,8-tetrahydro-2-naphthoxyethyl)-piperidine, HCl. M.p. 186.6°C. Reaction
30 time 3.5 h.
- (-) trans 4-(4-Fluorophenyl)-1-hexyl-3-(5,6,7,8-tetrahydro-2-naphthoxyethyl)-piperidine, HCl. M.p. 146.7°C. Reaction
35 time 4 h. The crude product was purified on a silicagel column with CHCl₃/CH₃OH (9/1) as eluent.

(-) trans 1-Ethyl-4-(4-Fluorophenyl)-3-(5,6,7,8-tetrahydro-2-naphthoxymethyl)-piperidine, HCl. M.p. 217.0°C. Reaction time 24 h. The crude product was purified on a silicagel column with $\text{CHCl}_3/\text{CH}_3\text{OH}$ (9/1) as eluent.

5

Example 6

(-) trans 3-(2-Benzothiazolylthiomethyl)-4-(4-fluorophenyl)-1-methylpiperidine, HCl was prepared by refluxing a mixture of 5g benzothiazol-2-thiol, 7,1g (-) trans-(3-chloromethyl)-4-(4-fluoromethyl)-1-methylpiperidine and 5g potassium carbonate in ethanol for 24h. Acetone/ether was added, the mixture filtered and the filtrate evaporated to dryness. The residue was extracted from NaOH/ether, the ether layer dried with K_2CO_3 , acidified with conc. HCl to pH2, and evaporated to dryness. The resulting oil was crystallized from acetone/ether. m.p. 204.2°C.

10

15

20

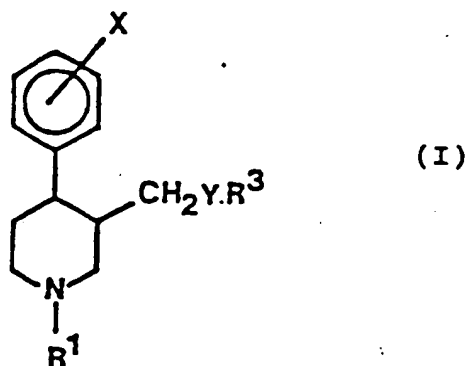
25

30

35

CLAIMS.

1. Piperidine compounds having the general formula I



wherein

R^3 is 3,4-methylenedioxyphenyl, phenyl, naphthyl or benzothiazolyl which are optionally substituted with one or more C_{1-6} -alkyl, C_{1-6} -alkoxy group, C_{3-8} -cycloalkyl, C_{3-5} -alkylene or benzyloxy,

R^1 is straight or branched C_{5-8} -alkyl, C_{1-8} -alkoxy- C_{4-8} -alkyl, C_{4-7} -cycloalkyl, phenoxy- C_{3-8} -alkyl, C_{4-8} -alkenyl, or C_{4-8} -cycloalkylalkyl, or R^1 may also be hydrogen or C_{1-4} -

alkyl when R^3 is phenyl substituted with two or more of C_{3-8} -cycloalkyl, benzyloxy or C_{3-5} -alkylene, or when R^3 is naphthyl or benzothiazolyl substituted with two or more C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{3-8} -cycloalkyl, benzyloxy or C_{3-5} -alkylene,

X is hydrogen or halogen, and wherein

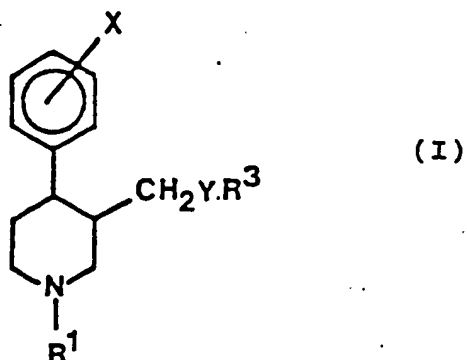
Y is O or S

and a salt thereof with a pharmaceutically acceptable acid.

2. A compound of claim 1 which is (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-pentylpiperidine hydrochloride

CLAIMS.

1. Piperidine compounds having the general formula I



wherein

R^3 is 3,4-methylenedioxyphenyl, phenyl, naphthyl or benzothiazolyl which are optionally substituted with one or more C_{1-6} -alkyl, C_{1-6} -alkoxy group, C_{3-8} -cycloalkyl, C_{3-5} -alkylene or benzyloxy,

R^1 is straight or branched C_{5-8} -alkyl, C_{1-8} -alkoxy- C_{4-8} -alkyl, C_{4-7} -cycloalkyl, phenoxy- C_{3-8} -alkyl, C_{4-8} -alkenyl, or C_{4-8} -cycloalkylalkyl, or R^1 may also be hydrogen or C_{1-4} -alkyl when R^3 is phenyl substituted with two or more of C_{3-8} -cycloalkyl, benzyloxy or C_{3-5} -alkylene, or when R^3 is naphthyl or benzothiazolyl substituted with two or more C_{1-6} -alkyl, C_{1-6} -alkoxy, C_{3-8} -cycloalkyl, benzyloxy or C_{3-5} *alkylene*

X is hydrogen or halogen, and wherein

Y is O or S

and a salt thereof with a pharmaceutically acceptable acid.

2. A compound of claim 1 which is (-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxyethyl)-1-pentylpiperidine hydrochloride

3. A compound of claim 1 which is (+)-trans-4-phenyl-3-(3,4-methylenedioxyphenoxymethyl)-1-penthylpiperidine hydrochloride

5 4. A compound of claim 1 which is (-)-trans-4-(-4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-1-pentylpiperidine hydrochloride

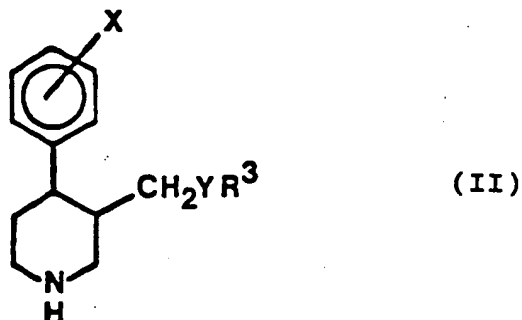
10 5. A compound of claim 1 which is (-)-trans-4-(-4-fluorophenyl)-3-(5,6,7,8-tetrahydro-2-naphthoxymethyl)-1-pentylpiperidine hydrochloride

6. A method of preparing a compound according to claim 1, CHARACTERIZED in:

15

a) reacting a compound having the general formula II

20



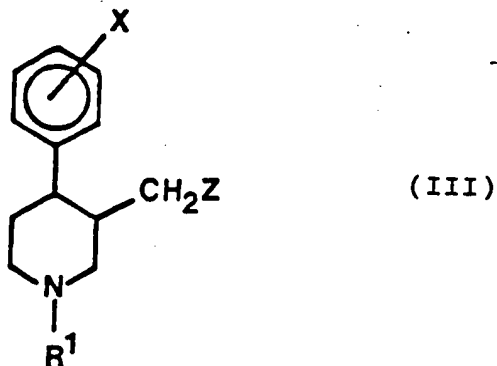
25

wherein R^3 , X and Y have the meanings defined above, with a compound having the the general formula R^1-Z , wherein Z is a leaving group such as halogen and R^1 has the meaning defined above,

30

b) reacting a compound having the general formula III

35



wherein R^1 and X have the meanings defined above, and Z is a leaving group, with a compound having the the general formula R^3 -YH, wherein Y is O or S and R^3 has the meaning defined above.

7. A pharmaceutical composition suitable for use in preventing calcium overload in brain cells of mammals, including humans, comprising an amount of a compound of claim 1, or which is effective for inhibiting calcium uptake into brain cells together with a pharmaceutically-acceptable carrier or diluent.

8. A pharmaceutical composition according to claim 7 wherein it is in the form of an oral dosage unit containing 1-100 mg of the active compound.

For the Applicants,
DR. REINHOLD COHN AND PARTNERS
BY:

N. D. ...